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Priapism Secondary to Penile Metastasis: A Report of Two Cases and a Review of the Literature

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Malignancy metastasis to the penis is an uncommon clinicopathological entity. We present two cases of malignant priapism following penile metastasis, in which the diagnosis was established by core needle biopsy of the corpus cavernosum. Primary tumors were urothelial carcinoma of the urinary bladder in one case (the patient having concomitant high-grade prostatic adenocarcinoma) and prostatic adenocarcinoma in the other. The clinicopathological features of 51 previously reported cases of penile metastasis in the recent literature are reviewed.

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KEY WORDS: **metastatic carcinoma; penis; priapism**

INTRODUCTION

Priapism is a persistent, prolonged, and painful erection not associated with sexual stimulation. Malignancy metastasis to the penis is a rare cause of priapism. Other manifestations related to penile metastasis include local lesions (nodule, induration, or ulcer) and obstructive and irritative urinary symptoms. The appropriate diagnosis of such an uncommon condition requires a high index of suspicion and careful examination when following patients at risk, especially those with invasive genitourinary malignancy. We describe two cases of malignant priapism secondary to invasive urothelial (transitional cell) carcinoma of the urinary bladder and prostatic adenocarcinoma, respectively. Core-needle biopsy, complemented with immunohistochemical phenotypical characterization, was used to establish the diagnosis and allow discrimination of the primary source of metastasis in one patient with two primary malignancies. The clinicopathological features of 51 other cases (Table I) [1–31] reported in the recent literature are reviewed.

CASE REPORTS

Case 1

The subject was a 75-year-old Caucasian with recurring high-grade, solid, and papillary urothelial carcinoma of the bladder, with evidence of invasion within the muscularis propria and vascular invasion at the level of the lamina propria, originally diagnosed in January 1995 (Fig. 1). He underwent bilateral pelvic lymph node dissection and a cystoprostatectomy with an ileal conduit construction in June 1995. Pathological examination revealed multiple regions of papillary high-grade urothelial carcinoma of the bladder with invasion of the lamina propria. Incidentally, a small-sized (0.8 × 0.8 × 0.5 cm, <5% total volume) prostatic adenocarcinoma, Gleason's histologic score 9/10, confined within the fibromuscular capsular boundary, was found in the peripheral zone. Lymph nodes and seminal vesicles were negative for neoplasia. In March 1996, he presented to the emergency room describing a 6-week history of increasing penile pain with edema and rigidity of the penile shaft not associated with sexual stimulation. His ileal conduit was functioning well and he denied any bone pain or weight loss. On examination, the penis was erect and the coronal

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TABLE I. Cases of Penile Metastasis Reviewed*

Primary neoplasm	Age (yr)	Presentation[a]	Site of penile metastasis	Other metastasis	Duration[b] (months)	Diagnostic methods	Treatment[c]	Survival[d] (months)	References
Genitourinary tract									
Prostate									
Adenocarcinoma	73	Priapism, urinary symptoms, Retention	Corpus cavernosum	Bone	24	Bx	Palliative	2	1
	77	Painless nodule	Glans	None	3	Bx	Hormonal, surgery	7+	2
	57	Urinary symptoms Painful erection	Glans	Bone	2	Bx	Hormonal, surgery	84+	3
	53	—	Glans	Liver, bone	3	Bx	Palliative	1	4
	61	—	Corona, base	Pelvis	12	Bx	Chemo, radiation	60	4
	76	Priapism	Corpus cavernosum	Pleura, lung, liver	4	Bx	Hormonal	8	5
	78	Glans edema	Glans	Lung, bone	48	Bx	Hormonal	16+	5
	68	Foreskin redness	Corona	—	36	Bx	Hormonal	24+	6
	69	Urinary symptoms, retention, nodule	Corpus cavernosum, urethra, glans	Bone	84	Bx	Surgery	2+	7
	72	Priapism, urinary symptoms Retention	Corpus cavernosum, urethra	Multiple	192	Biopsy, CT, cystoscopy	Radiation, hormonal	2+	7
	70	Painful nodule, urethral hemorrhage	Corpus cavernosum, urethra	Bone	10	Bx	Hormonal	—	8
	75	Priapism, nodule	Corpus cavernosum	Multiple	48	Biopsy, MRI, Cvgm	Hormonal, palliative	4	9
	68	Nodule, urinary symptoms, urethral hemorrhage	Glans, urethra	None	24	Biopsy, cystoscopy, urethrogram	Hormonal	14	10
	62	Urinary symptoms, retention	Urethra	Bone	7	Biopsy, cystoscopy, urethrogram	hormonal	17	10
	77	Urinary symptoms	Urethra	None	0	Biopsy, cystoscopy	Hormonal	—	10
	74	Ulcer, edema	Skin	Multiple	0	Biopsy	None	12+	11
	83	Priapism, pain, nodule, Urinary symptoms, retention	Corpus cavernosum	None	8	Biopsy	Hormonal	12+	Current case 2
Squamous cell Ca	79	Painless nodule	Glans	None	1	Biopsy	Surgery	4+	12
Mixed urothelial Ca, adenocarcinoma	63	Priapism, nodule, pain	Corpus cavernosum	Lung	7	Biopsy	Hormonal, chemo, radiation	1	13

(*Continued*)

TABLE I. Cases of Penile Metastasis Reviewed* (*Continued*)

Primary neoplasm	Age (yr)	Presentation[a]	Site of penile metastasis	Other metastasis	Duration[b] (months)	Diagnostic methods	Treatment[c]	Survival[d] (months)	References
Urinary bladder									
Urothelial Ca	69	—	Corona	Lung, bone	36	Biopsy	Palliative	0.2	4
	60	—	Corpus cavernosum	Bone	3	Biopsy	Chemo, radiation	8	4
	66	Ulcer	Glans	Incision scar, Lung	2.5	Biopsy	Surgery, radiation	5.5	5
	65	Urinary symptoms	Corpus cavernosum	None	29	Biopsy	Chemo	22+	14
	48	—	Corpus cavernosum, Urethra	None	7	Biopsy	Chemo	20+	14
	54	—	Corpus cavernosum, corpus spongiosum, Glans, urethra	None	12	Biopsy	Chemo, surgery	24+	14
	66	Priapism	Corpus cavernosum	Bone	7	Biopsy	Chemo	4	14
	72	Nodule, pain, urinary symptoms	Corpus cavernosum	Lung	3	Biopsy, Cvgm	Radiation	10+	15
	68	Nodule, urethral hemorrhage	Urethra	Lung	29	Clinical	Radiation	4+	15
	73	Nodule, pain	Corpus spongiosum	Multiple	33	Biopsy	Surgery	6	15
	70	Nodule	Corpus cavernosum	Bone	2	Biopsy	Surgery, chemo	—	16
	75	Nodule, pain	Glans	None	63	Aspiration cytology	Palliative	2	16
	67	Nodule	Urethra	None	0	Biopsy	Chemo, surgery	3	17
	80	Priapism, pain, edema	Corpus cavernosum	Lung	192	Autopsy	Palliative	3	18
	75	Priapism, edema	Corpus cavernosum	Bone	13	Biopsy	Palliative	4	Current case 1
Adenocarcinoma	74	Nodule, pain	Corpus cavernosum	Multiple	72	Aspiration cytology	surgery	—	16
Signet-ring/ urothelial/ adenocarcin-oma	67	Urinary symptoms, nodule	Corpus cavernosum	Pelvis, lung	1	Biopsy	Chemo	3	19
Kidney									
Renal cell Ca									
Right	60	Painless nodule	Corpus spongiosum, urethra	L. Kidney, R. Hemi-scrotum	72	Biopsy	Surgery	8	20
Right	49	Nodule	Corpus cavernosum	None	84	Biopsy	Surgery	6+	21
Right	76	Priapism	Corpus spongiosum	None	0	Biopsy	Surgery, radiation	5+	22
Left	60	Priapism, retention	Corpus cavernosum	None	0	Biopsy, CT	Immuno-therapy	3	23
Right	56	Nodule	Corpus cavernosum	Para-aortic lymph node, IVC	0	Biopsy	Immuno-therapy, chemo	—	24

(*Continued*)

TABLE I. Cases of Penile Metastasis Reviewed* (*Continued*)

Primary neoplasm	Age (yr)	Presentation[a]	Site of penile metastasis	Other metastasis	Duration[b] (months)	Diagnostic methods	Treatment[c]	Survival[d] (months)	References
Ureter									
Urothelial Ca									
Right	63	Priapism, nodule, pain	Corpus cavernosum	Pelvis, para-aortic lymph node	11	Clinical	Radiation	6	15
Testis									
Teratoma/ embryonal Ca									
Right	32	Nodule	Corpus cavernosum	Lung	3	Aspiration cytology	Chemo	24+	25
Teratoma									
Left	45	Nodule	Corpus cavernosum	Para-aortic lymph node	1.5	Sonography	Surgery, chemo	14+	26
Gastrointestinal tract									
Rectum									
Adenocarcinoma	60	—	Corona	Lung, bone, retroperitoneum	15	Biopsy	Chemo, radiation	13	4
Cecum									
Adenocarcinoma	70	—	Urethra	Pelvis	48	Biopsy	Surgery	10	4
Sigmoid									
Adenocarcinoma	71	Nodule	Glans	Pelvic	48	Biopsy	Palliative	5	20
	77	Nodule	Corpus cavernosum	Inguinal canal	25	Biopsy	Surgery	—	27
	52	Nodule	Corpus cavernosum	—	3	Sonography CT, MRI	Surgery	—	28
Other									
Lung									
Squamous cell Ca	65	Priapism	Corpus cavernosum	Abdominal visceral	0	Biopsy	Radiation	4.5	6
	67	Priapism, retention	Corpus cavernosum, corpus spongiosum, urethra, glans	Multiple	18	Biopsy	Palliative	1	29
	67	Nodule	Corpus cavernosum	Adrenal	24	Biopsy	—	—	30
Larynx									
Squamous cell Ca	64	Nodule, urinary symptoms	Glans	Lung, liver	10.5	Biopsy	Radiation	3	31

*—, information unavailable; +, more than; Cvgm, cavernosography; Chemo, chemotherapy; Bx, biopsy; Ca, carcinoma.
[a]Nodule includes such presentations as mass, and induration. Urinary symptoms include incontinence, hematuria, and obstructive and irritative symptoms.
[b]Interval from diagnosis of the primary malignacy to the presentation of penile metastasis.
[c]Surgery includes local excision of metastic tumor and penectomy. Hormonal therapy includes surgical and chemical castration.
[d]Interval from presentation of penile metastasis to death.

shaft was boggy and swollen. Palpation along the length of the penis and the scrotum elicited pain and revealed an indurated shaft and flaccid glans. Digital rectal examination revealed no sign of tumor invasion; such a finding was later confirmed on transrectal ultrasonographic examination and pelvic floor biopsies. His serum prostate-specific antigen (PSA) level was less than 0.2 ng/ml. Core-needle biopsy sampling of the corpus cavernosum revealed clusters of neoplastic cells characterized by a high nuclear/cytoplasmic ratio, nuclear hyperchromasia, occasional nucleoli, and evidence of individual cell necrosis (Figs. 2, 3b). Tumor cells were mostly localized

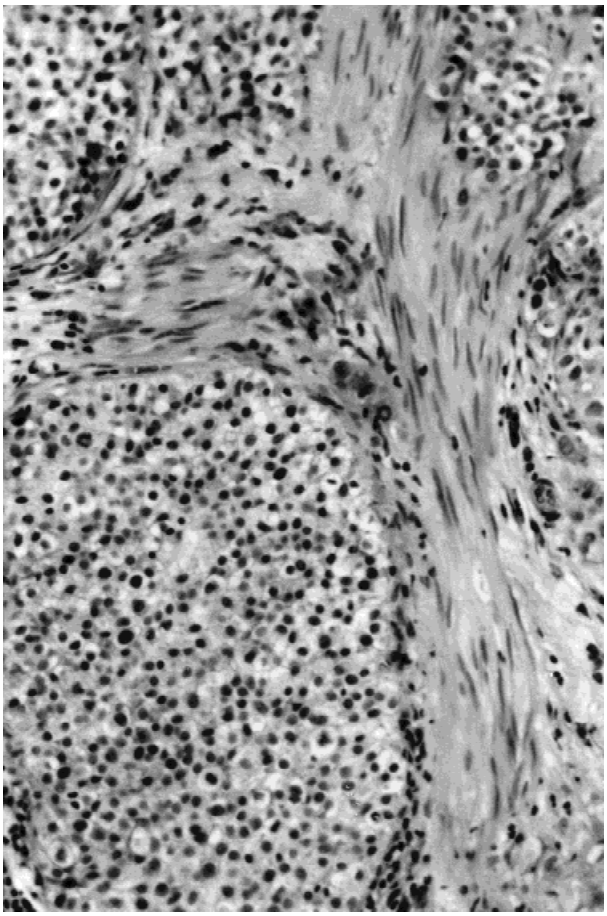

Fig. 1. Biopsy of primary bladder tumor (case 1). Solid sheets of high-grade urothelial carcinoma with muscle entrapment at the level of muscularis propria (H&E, ×100).

within cavernous vascular spaces, with a few admixed red blood cells (Fig. 2). Tumor cells were intensely immunoreactive for cytokeratin AE1/AE3 (Boehringer Mannheim; dilution 1:800) and negative for PSA (Dakopatts; dilution 1:5,000) (Fig. 3a,b), sustaining the hypothesis of an epithelial/urothelial tumor phenotype. Furthermore, cytokeratin staining confirmed the presence of isolated tumor cells within the fibromuscular stroma of the corpus cavernosum (Fig. 3a). Metastatic work-up revealed extensive metastatic bone disease on nuclear bone scan, while chest radiograph and liver function tests were within normal limits. His general condition deteriorated rapidly. In view of his extensive bone metastasis, the patient was managed conservatively with pain control and died 4 months after developing symptoms of malignant priapism.

Case 2

The subject, an 83-year-old Caucasian, presented in October 1995 with progressive obstructive urinary symptoms. His serum PSA level was 61.7 ng/ml, and transrectal biopsy of the prostate revealed an adenocarcinoma of the prostate, Gleason's histologic score 9/10, involving 80–85% of sampling and with invasion of periprostatic soft tissue. Metastatic work-up, including a nuclear bone scan and chest X-ray, was negative. After presentation of treatment options, the patient chose to have hormonal therapy with Goserelin acetate and a transurethral resection of the prostate, which was performed in January 1996, to permit voiding. More than 50% of the prostatic tissue was involved by an adenocarcinoma of the prostate, Gleason's histologic score 9/10, with suburethral involvement and evidence of vascular invasion. In May 1996, the patient presented to the emergency room with a 2-day history of gross hematuria and urinary retention. The patient also complained of painful rigidity of the penis not associated with sexual stimulation. On examination, the penis was partially erect with a 4 × 2 cm area of induration on the shaft. A suprapubic urinary catheter was inserted to relieve the urinary obstruction. On cystoscopic examination, the penile urethra and verumontanum appeared normal. There was an obstruction in the prostatic fossa secondary to tumor invasion. Core-needle biopsy sampling of the corpus cavernosum revealed clusters of malignant cells mostly confined within cavernous vascular spaces. The tumor had a solid pattern with abortive glandular differentiation and focal necrosis, and showed cytoplasmic coexpression of cytokeratin AE1/AE3 and PSA, confirming its prostatic epithelial phenotype. The presence of additional tumor cells within the fibromuscular stroma of the corpus was enhanced by cytokeratin staining. The patient continued on hormonal therapy and opted for long-term urinary diversion with a suprapubic urinary catheter and pain control. In January, 1997, 13 months after commencing hormonal therapy, his PSA decreased to 4.0 ng/ml. He is alive more than 12 months since presenting with malignant priapism.

DISCUSSION

The first documented case of penile metastasis was reported in 1870 by Eberth [32]. By July 1997, 460 cases had been reported worldwide. The true incidence, however, is probably higher, as many cases are unrecognized, with 12% of cases of penile metastatic tumor being symptom free [33]. Even in postmortem examination, unless specifically sought, penile metastasis will probaly be missed. Another possible reason to suspect that the actual incidence is higher is that cases without any ''unusual'' clinical features are less likely to be reported.

In previous reviews [33–39], including our series, genitourinary tract carcinomas were found to be the most common type of solitary malignancy to metastasize to the penis (Tables I and II). Among these, prostatic adenocarcinoma (26–32% in previous reviews) and urothelial carcinoma of the bladder (27–35% in previous reviews) are the most common type of primary cancer,

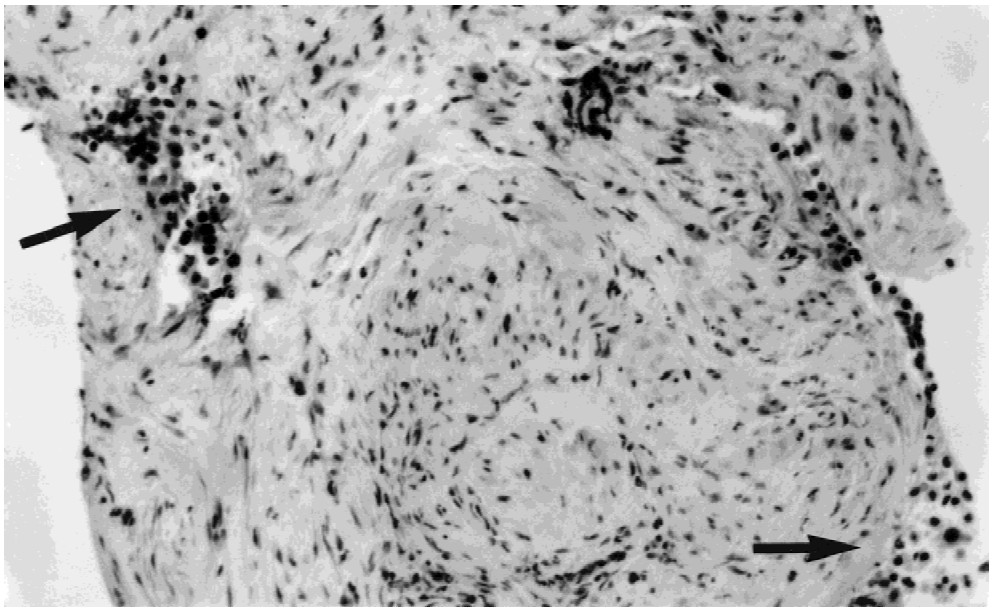

Fig. 2. Core biopsy specimen of penile corpus cavernosum showing small clusters of malignant cells (arrows) predominantly localized within the vascular spaces (H&E, ×100).

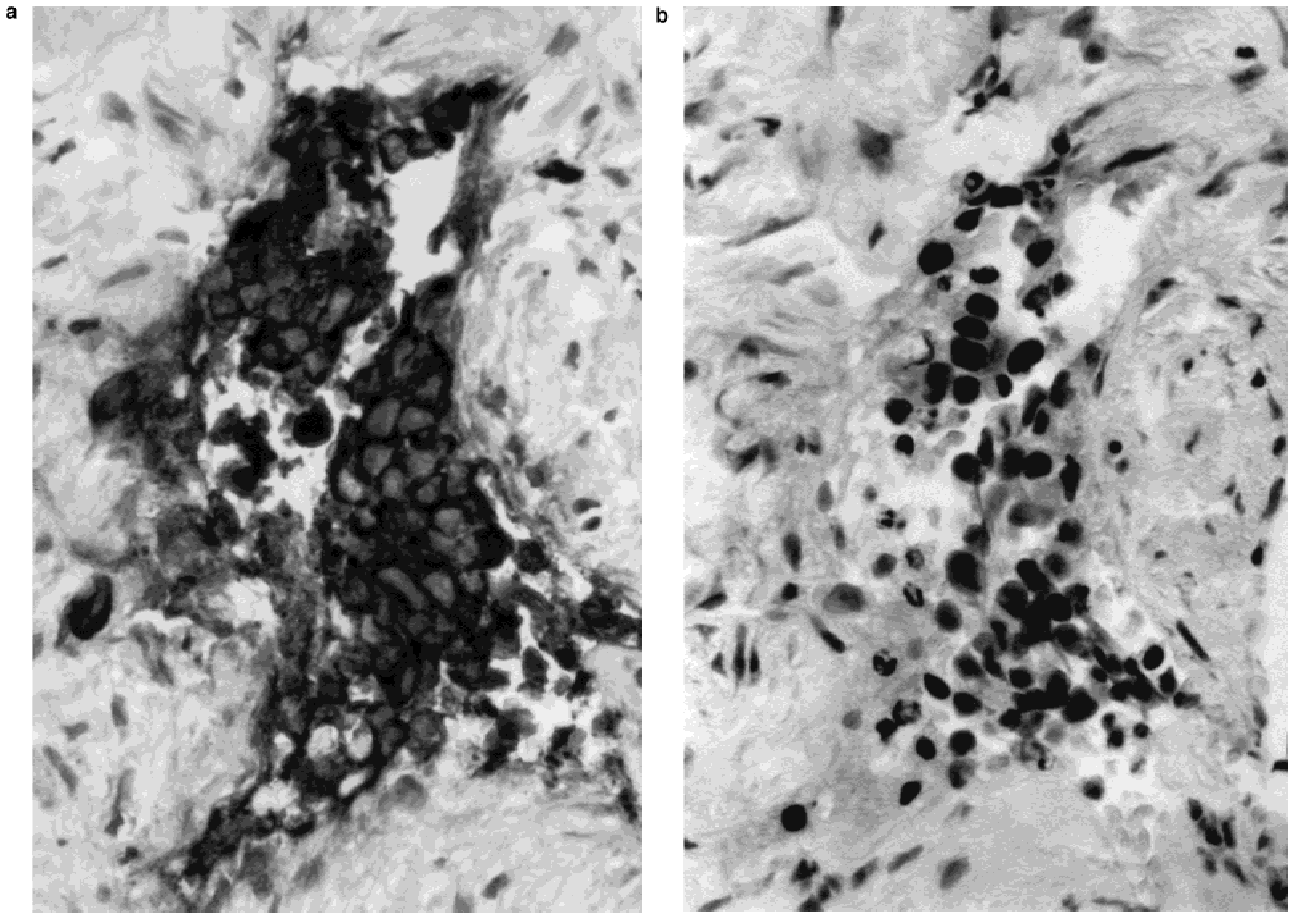

Fig. 3. Biopsy of corpus cavernosum. **a:** Strong cytoplasmic immunoreactivity for cytokeratin confirms the epithelial phenotype of tumor cells and enhances the presence of a few isolated tumor cells within the fibromuscular stroma of corpus cavernosum (avidin-biotin peroxidase complex, ×250). **b:** Negative staining for prostate-specific antigen supports the hypothesis of a urothelial, rather than prostatic, origin of tumor cells (avidin-biotin peroxidase complex, ×250).

TABLE II. Primary Site of Tumor in Reviewed Cases of Penile Metastasis

Site	No. of cases	%	References
Genitourinary tract			
Prostate			
Adenocarcinoma	17	32	1–11, current case 2
Squamous cell Ca[a]	1	1.9	12
Mixed	1	1.9	13
Urinary bladder			
Urothelial Ca	15	28.3	4, 5, 14–18, current case 1
Adenocarcinoma	1	1.9	
Signet-ring/urothelial/ adenocarcinoma	1		19
Kidney			
Renal cell Ca	5	9.4	20–24
Ureter			
Right (Urothelial Ca)	1	1.9	15
Testis			
Right (Teratoma/ embryonal Ca)	1	1.9	25
Left (Teratoma)	1		26
Gastrointestinal tract			
Rectum			
Adenocarcinoma	1	1.9	4
Cecum			
Adenocarcinoma	1	1.9	4
Sigmoid			
Adenocarcinoma	3	5.7	20, 27, 28
Other			
Lung			
Squamous cell Ca	3	5.7	6, 29, 30
Larynx			
Squamous cell Ca	1	1.9	31

[a]Ca, carcinoma.

TABLE III. Initial Presentation in Reviewed Cases of Penile Metastasis

Presentation	No. of cases	%
Nodule[a]	27	51
Priapism	14	27
Urinary symptoms[b]	14	27
Pain	9	17
Retention	7	13
Skin lesion[c]	6	11

[a]Includes such presentations as mass and induration.
[b]Includes urethral hemorrhage, hematuria, incontinence, and irritative and obstructive symptoms.
[c]Includes edema and ulcer.

followed by renal cell carcinoma (8–11% in previous reviews) and testicular germ cell neoplasia (3–10% in previous reviews). Colorectal adenocarcinoma is also commonly found as a source of penile metastasis. Other less common primaries reported in the literature include carcinoma of the lung, nasopharynx, or pancreas, hepatocellular carcinoma, malignant melanoma, and high-grade (Burkitt) malignant lymphoma.

In both of our cases, vascular invasion was observed in the primary tumor. Such an observation has been considered a poor prognostic factor in urothelial carcinoma [40, 41] and prostatic adenocarcinoma [42], although this issue remains controversial [43]. In most of the previously reported cases of penile metastasis in our review, there was no specific mention of the presence or absence of vascular invasion in the primary tumor. With such limited information, the relationship between vascular invasion (in the primary tumor ab initio) and subsequent tumor embolization within the corpus cavernosum is unclear.

In both of our patients, the diagnosis of penile metastasis was histopathologically confirmed on core-needle biopsy of the corpus cavernosum. Although diagnostic modalities such as corpora aspiration cytology, cavernosography, magnetic resonance imaging, and computer tomography have been described, the merit of core-needle biopsy lies in its more reliable assessment of the presence of malignant cell infiltration and the histological extent of invasion. Furthermore, in selected cases, it allows immunophenotypical characterization of the tumor cell infiltrate to confirm the precise nature of the malignancy (e.g., case 1 with two primary malignancies).

The route of tumor metastasis to the penis remains uncertain. For an organ with rich and interconnected lymphatic and venous drainage from the various pelvic organs via the pudendal, vertebral, and Batson venous plexus, and in such close proximity to pelvic and abdominal organs, which are frequent sites of malignancy, the incidence of secondary cancer in the penis is expected to be much higher. Hashimoto et al.[44] speculated that alterations of vascular flow pattern during erection and detumescence may partially account for the difficulty of carcinoma cell implantation. Possible mechanisms whereby tumors metastasize to the penis have been proposed and reviewed by various authors [33–35]. The common routes are direct extension of the primary tumor to the penis, antegrade arterial dissemination from the distant primary tumor, seeding from instrumentation (from transurethral resection of the prostate or internal urethrotomy), retrograde lymphatic and venous spread, and extension along the nerves.

Priapism is considered to be the initial mode of clinical presentation in 20–53% cases [33,35] of penile metastasis. In our series reviewed, 27% of cases had priapism as a presenting feature (Table III). The pathophysiology of malignant priapism is thought to be due to tumor infiltration of the corpora and/or neoplastic invasion of venous drainage leading to stasis and thrombosis. Irritation of the neural pathways of erection may be another mechanism of malignant priapism [45]. Clinicians must be cautious in distinguishing true priapism from ‘‘pseu-

dopriapism,'' in which rigidity and edema are secondary to nodular metastasis rather than actual tumescence of the corpora cavernosa. Other manifestations of penile metastasis include local lesions (nodule, mass, induration, edema, cutaneous alteration or ulcer)[46] and urinary symptoms.

The prognosis following penile metastasis is generally poor. Metastasis to other organs was found in 75% of patients in our review, and in more than two-thirds of cases in other reviews [33,46]. In a previous review [47], the mean duration of survival following the diagnosis of penile metastasis from primary urothelial carcinoma of the bladder was estimated to be 3.9 months with a range of 0–20 months. In our series reviewed, three patients [14] had survived longer than 20 months after chemotherapy. In primary prostatic adenocarcinoma, survival of more than 7 years has been reported [3,48]. The survival time of patients with penile metastasis from colorectal adenocarcinoma appears to be longer [49–51], including a patient who survived for 9 years after local surgical excision.

Various treatment modalities for penile metastasis are described in the literature. For lesions confined to the glans or the shaft without extension into the pelvis/pelvic diaphragm, total penectomy is occasionally performed for intractable pain or severe urinary tract symptoms caused by tumor infiltration into the corpora cavernosa [52]. When the extent of tumor is beyond surgical extirpation, radiation and chemotherapy, or palliative care in certain cases, have been employed. The choice of treatment modalities is based on anecdotal information and without any prospective trials. Thus no mode of therapy has been convincingly proved to be superior in prolonging patient survival. It appears that survival depends more on the general clinical status of the individual, the nature of the primary tumor, the extent of malignancy, and the presence of concurrent metastases elsewhere, than on the modality of treatment used. A similar opinion is shared by other authors [33]. Proper management of patients with such diagnosis should thus be individualized.

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